REMARKS

The present Office Action is in response to the Appellants' Brief on Appeal filed March 24, 2004. In the Office Action, the Examiner withdrew the finality of the previous Office Action (Paper No. 17), but maintained rejection of the claims "for the same reasons as set forth in the previous Office Action."[1/] (Paper No. 06272004 at 2.) In addition, the Examiner presented new grounds for rejection. (*Id.* at 5-8).

Obviousness Rejections

Claim 8 was rejected under 35 USC § 103 as unpatentable over Mitchell, U.S. Patent No. 4,588,717 ("Mitchell"), Kamarei *et al.*, U.S. Patent No. 4,879,312 ("Kamarei"), and Miettinen *et al.*, WO 92/19640 ("Miettinen") in the previous Office Action. (Paper No. 17 at 3.)

For the reasons set forth below the rejection, respectfully is traversed.

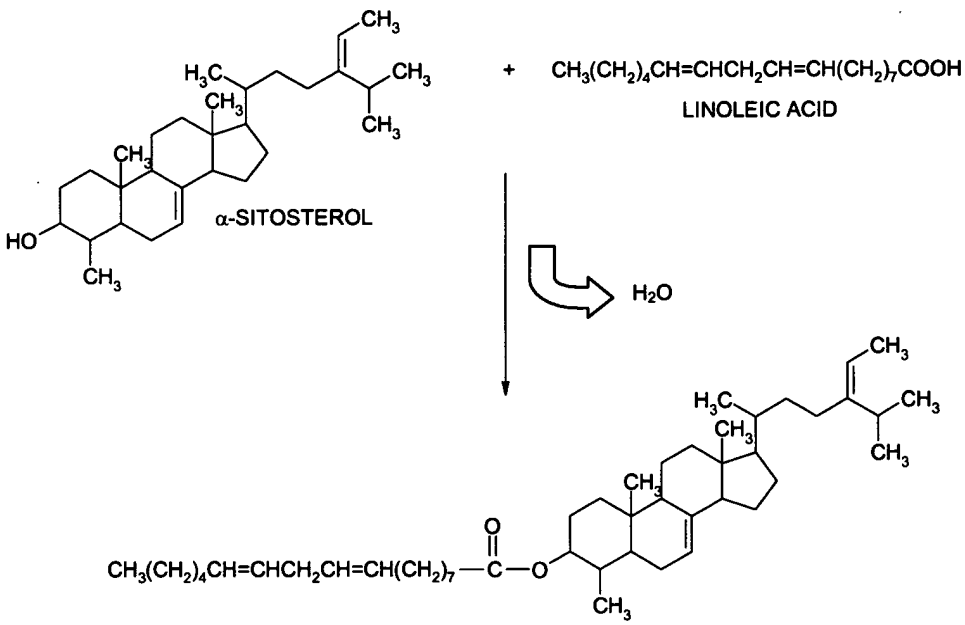
Mitchell discloses a broad range of vitamin supplements containing phytosterol esters, substituted fructose compounds, and antitrypsin enzymes, as well as, methods of making same. (Col. 1, lines 7-12.) The disclosed phytosterol ester supplements are designed to provide a "method for administering steroids and hormones to humans and other animals without directly introducing the hormones and steroids into the blood stream or digestive tract," which would have undesirable effects, including androgenic effects, acne, voice changes, poor absorption and the generation of toxic byproducts, *etc.* (*Id.*, lines 46-65.)

1/ In view of the Examiner's withdrawal of the finality of the previous Office Action and the reopening of prosecution, the Examiner's comments as to the Appellants' Brief on Appeal (Paper No. 06272004 at 2-4) are moot. Should we be required to appeal the same rejections yet again, we will address the Examiner's comments at that time.

Mitchell broadly discloses fatty acid esters of phytosterols, such as sitosterol, stigmasterol, taraxasterol and mixtures thereof. (Col. 3, lines 26-36 and col. 5, lines 48-51.) Mitchell broadly defines the phytosterol portion of the disclosed esters to include "all phytosterols" and derivatives thereof. (Col. 5, lines 26-28.)

Mitchell defines the fatty acid portion of the disclosed esters to include "***any*** fatty acid having from about 18 to about 20 carbon atoms in the main carbon chain and at least two carbon-to-carbon double bonds, in addition to terminal carboxyl and methyl groups." (Emphasis added.) (Col. 6, lines 2-8.) Mitchell recognizes that "many fatty acids are included within this category." (*Id.*) In preferred embodiments, Mitchell identifies linoleic acid (C_{18}, ω-6-fatty acid), linolenic acid (C_{18}, ω-3-fatty acid), and arachidonic acid (C_{20}, ω-6-fatty acid) as the fatty acid source for the phytosterol esters. (Col. 3, lines 26-36.) Mitchell further includes fatty acids having less than 18 carbon atoms and more than 20 carbon atoms within the scope of the invention, but notes "that phytosterol esters made with such fatty acids tend to have less utility in achieving the purposes of the present invention" (*i.e.*, delivering steroid and hormone precursors to the body). (Col. 6, lines 9-15.)

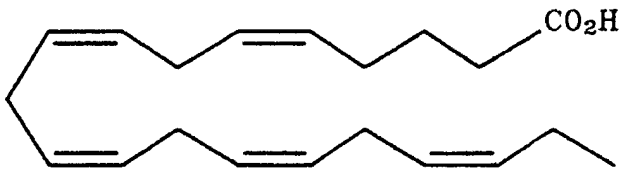
Mitchell describes the reaction between a phytosterol and a fatty acid as a "condensation" reaction and provides a characteristic reaction scheme, which is said to be "essentially the same" reaction between "any given phytosterol" and "any given fatty acid."



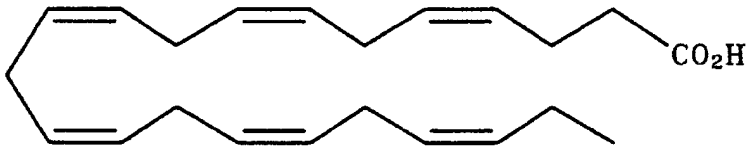
(Col. 8, lines 33-37 and Equation 1).

Mitchell provides 75 examples of the phytosterol ester vitamin supplement. In those examples, however, only three fatty acids are exemplified as part of the phytosterol ester: linoleic acid (Examples 1-25), linolenic acid (Examples 26-50), and arachidonic acid (Examples 51-75). Likewise, in the 75 examples, only three phytosterols are exemplified as the phytosterol component of the ester: sitosterol, stigmasterol, and taraxasterol.

Kamarei discloses a "method for provoking or enhancing" the formation of new blood vessels, a process called "angiogenesis," in a patient by administering "an angiogenically effective amount of an angiogenically active ω-3 polyunsaturated fatty acid." (Col. 3, lines 13-17.) Kamarei discloses that "especially preferred" ω-3 polyunsaturated fatty acids are EPA and DHA. (*Id.*, lines 18-19.) Kamarei sets forth the chemical structures of EPA and DHA in Fig. 1:



EPA



DHA

Kamarei discloses that a diet rich in ω-3 fatty acids has a beneficial effect in humans, including reduction of plasma cholesterol and triglyceride levels. (Col. 2, lines 39-41.) Kamarei also observes that EPA reportedly was known to reduce triglyceride and very low density lipoprotein ("VLDL") serum levels. But, when administered to a patient, EPA caused bleeding time to increase and the ability of platelets to aggregate to decrease. (*Id.*, lines 54-59.) Kamarei also discloses that it was known to use of a combination of EPA or DHA and a linoleic acid derivative in the treatment of thrombo-embolic conditions. (*Id.*, lines 63-68.) Kamarei further discloses that it was known to administer "mixtures of EPA and DHA/linoleic acid derivatives ... in food form." (Col. 3, lines 2-5.)

Miettinen discloses β-sitostanol fatty acid ester compounds and mixtures that lower serum cholesterol levels. (Abstract and page 6, lines 8-34.) Miettinen discloses that a β-sitostanol mixture is esterified with "different fatty acid ester mixtures by a commonly known chemical interesterification technique." (Page 6, lines 26-30.)

Miettinen further discloses that the β-sitostanol fatty acid esters may be added to food and convey advantages in "national nutrition and in the treatment of hypercholesterollemia." (Page 8, lines 30-34.)

Miettinen also discloses that the described compounds/mixtures have wide applications because their physical properties may be modified easily by altering the fatty acid composition of the mixture. Miettinen discloses that "the fatty acid composition of the β-stanol fatty acid ester mixture can be selected so as to contain large amounts of monoenes and polyenes, whereby its efficacy in lowering the cholesterol levels in serum are enhanced." (Page 9, lines 21-30.)

In addition to mixtures of rapeseed oil, Miettinen discloses that a methyl ester or a mixture of methyl esters of any vegetable oil, "especially" C_{2-22} fatty acids from a vegetable oil, may be used to esterify the β-sitostanol. (Page 10, lines 20-24; *see also* page 6, lines 32-34.)

In making the rejection, the Examiner asserted that Mitchell discloses "vitamin supplements containing phytosterol esters such as fatty acid esters of sterol, stigma sterol [sic] and taraxasterol, in various combinations." (Paper No. 17 at 3.) The Examiner also asserted that Mitchell discloses that "[f]atty acid[s] hav[ing] about 18-20 in addition to two carbon atoms of terminal carboxyl and methyl groups (lines 2-15, col. 6) and at least two double bonds such as arachidonic acid, linoleic acid and linolenic acids are used to make phytosterol esters (see lines 21-58, col. 3; lines 43-65, col. 5; equation 1 and lines 1-11 in col. 8)." (*Id.*) The Examiner also asserted that Mitchell discloses that "the reaction between any given phytosterol and any given fatty acid is essentially the same...." (*Id.*)

The Examiner asserted that Kamarei discloses "that a diet rich in omega-3-fatty acids has beneficial effects in humans...." (*Id.* at 4.) The Examiner also asserted that Kamarei discloses that "one of n-3 PUFA *i.e.* eicosapentaenoic acid (EPA) and DHA reduces triglyceride and very low-density lipoprotein (VLDL) serum levels and reduces whole blood viscosity." (*Id.*)

The Examiner asserted that Miettinen discloses "a composition of b-sitostanol fatty acid ester mixture or fatty acid ester mixture" and that the "physical properties of [the] mixture can be modified easily by altering the fatty acid composition of the mixture." (*Id.*) The Examiner further asserted that Miettinen discloses a "fatty acid mixture containing 2-22 carbon atom and esterification of sitostanol." (*Id.*)

The Examiner acknowledged, however, that claim 8 differs from the cited documents in claiming a "phytosterol ester compound produced by the reaction of a phytosterol and two specific fatty acids" – EPA (a C_{20}, ω-3-fatty acid) and DHA (a C_{22}, ω-3-fatty acid). (*Id.* at 5) The Examiner asserted that "it would be obvious to ... employ" a phytosterol composition in combination with an ω-3-fatty acid becase these agents "are known individually" for lowering plasma cholesterol and triglyceride levels. (*Id.*) The Examiner concluded that claim 8 is nothing more than a combination of prior art teachings:

> Instant claim is a selection of prior art teachings as EPA and DHA contain 20 and 22 carbons respectively which is taught by the prior art .... (*Id.*)
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> * * *
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> All ingredients of the instant invention are taught by the prior art for the same use. (*Id.* at 6.)
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> * * *

> The combination of agents, each of which known for the same purpose, is considered *prima facie* obvious. (*Id.*)

The Examiner asserted that the "motivation" (apparently to combine Mitchell, Kamarei and Miettinen) flows generally from "the prior art."

> Motivation is to prepare additional beneficial composition of sterols with unsaturated fatty acids such as omega-3-fatty acids, EPA, DHA, useful for lowering the cholesterol and triglyceride levels, because this use has been taught by the prior art for the said compositions. Preparation of supplemental vitamins, margarine and mayonnaise is taught by the prior art cited above. (*Id.*)

To reject a claim under 35 USC §103, the Examiner must show an unrebutted *prima facie* case of obviousness. *In re Deuel*, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). Obviousness must be based upon facts. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). When a conclusion of obviousness is not based on facts, it cannot stand. *Ex parte Porter*, 25 USPQ2d 1144, 1147 (BPAI 1992).

In combining references, the suggestion and motivation to make the combination must be based on "actual evidence" that must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) *abrogated on other grounds by In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). Moreover, "when the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the reference." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) *citing In re Yates*, 211 USPQ 1149, 1151 (CCPA 1981).

In the absence of a *prima facie* case of obviousness, an applicant who complies with the other statutory requirements is entitled to a patent. *In re Glaug*, 62

USPQ2d 1151, 1152 (Fed. Cir. 2002); and *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

The Examiner dismissed claim 8 as simply "a selection of prior art teachings." (Paper No. 17 at 5-6.) The Examiner concluded:

> Instant ***claim is a selection of prior art teachings*** as EPA and DHA contain 20 and 22 carbons respectively which is taught by the prior art .... (Emphasis added.) (*Id.* at 5.)
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> * * *
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> All ingredients of the instant invention are taught by the prior art for the same use. (*Id.* at 6.)

Whether or not each element of a claimed invention can be found in a "selection of prior art teachings," is however, irrelevant. In fact, most inventions are combinations of old elements. If the Examiner's "selection of prior art teachings" were the correct standard, very few applications would issue as patents. Unfortunately for the Examiner, her standard has been expressly repudiated by the Board of Patent Appeals and Interferences ("Board") and the Federal Circuit.

> As this court has stated, 'virtually all (inventions) are combinations of old elements....' If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, ***rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'*** *In re Rouffet*, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998) (Internal citations omitted.) (Emphasis added.)

The linchpin of the Examiner's position is that Mitchell and Miettinen disclose or suggest incorporating EPA or DHA into a phytosterol ester. To support this

position, the Examiner cited specifically to "lines 20-25 on page 10 of WO '640" (Miettinen) and generally to "US '717" (Mitchell). (Paper No. 17 at 5.)

The Examiner's reasoning is misguided in two respects. First, the cited portion of Miettinen discloses methyl esters or mixtures thereof from "***any*** vegetable oil, especially of fatty acids which contain approximately 2-22 carbon atoms." (Emphasis added.) (Page 10, lines 20-25). Thus, Miettinen does not disclose or suggest what the Examiner says it does – EPA and DHA. Rather, at best, Miettinen discloses a genus of fatty acids that contain "approximately 2-22 carbon atoms." (*Id.*) The Examiner failed to identify where in Miettinen EPA or DHA is specifically identified or suggested as being a good choice for esterification with sterol/stanols.

Second, with respect to Mitchell, the Examiner failed to cite to a specific portion of the patent, instead citing to "US '717" generally. (Paper No. 17 at 5.) Notwithstanding this lack of specificity, we note that Mitchell also does not disclose or suggest what the Examiner says it does – EPA and DHA. Rather, Mitchell discloses reacting a phytosterol with "virtually ***any*** fatty acid." (Col. 6, line 3.) Mitchell does specifically identify fatty acids having from "about 18 to about 20 carbon atoms," such as for example, "linoleic acid," "linolenic acid," and "arachidonic acid." (Col. 5, lines 55-66.) Mitchell also discloses that fatty acids "having less than 18 carbon atoms" or "more than 20 carbon atoms ... may be used," but that such fatty acids "tend to have less utility." (Col. 6, lines 9-15). Here too, the Examiner failed to identify where in Mitchell EPA or DHA is specifically identified or suggested as being a good choice for esterification with sterol/stanols.

Tellingly, when the Examiner applied her "selection of prior art teaching"

standard, she did not mention Kamarei, the only cited document that does specifically name EPA and DHA. (*See* Paper No. 17 at 5.) We submit that this omission was predicated on the Examiner's recognition that Kamarei, as a whole, is directed to "provocation or enhancement" of blood vessel growth (angiogenesis). Thus, one skilled in the art would not look to combine such a document with Mitchell or Miettinen, which disclose phytosterol esters.

In sum, the rejection – ***not*** the claims – is based on a "selection of prior art." (Paper No. 17 at 5.) The problem, as recognized by the Board and Federal Circuit, is that this rejection, like those in *Rouffet*, *West*, and *Sterner*, are devoid of any evidence to explain why one skilled in the art would make the particular selections proposed by the Examiner. Why would one have selected DHA or EPA based on the generic disclosure of ***any*** C_{2-22} fatty acid in Miettinen? Why would one have selected DHA or EPA based on the generic disclosure of ***any*** fatty acid in Mitchell or preferred fatty acids having about 18 to about 20 carbon atoms as exemplified by linoleic acid, linolenic acid, and arachidonic acid? Why would one have even considered DHA - a fatty acid containing 22 carbon atoms and within the scope of Miettinen - when Mitchell teaches that such compounds are not as useful as C_{18-20} fatty acids?

Absent such evidence, the only conclusion is that the Examiner used Applicants' specification as a blueprint to navigate from disclosures of "any fatty acid," C_{2-22} fatty acids, and C_{18-20} fatty acids cited in the documents applied by the Examiner to EPA and DHA as claimed. But, that is exactly the kind of hindsight reconstruction that is forbidden. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531-1532 (Fed. Cir. 1988) ("There must be a reason or suggestion in the art for selecting the procedure

used, other than the knowledge learned from applicant's disclosure."); *In re Bond*, 15 USPQ2d 1566, 1568-1569 (Fed. Cir. 1990) (The Board's holding "does not reflect the admonition of this court that '[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.' The Board's analysis is a classic case of hindsight reconstruction of the claimed invention."); and MPEP §2142 (8th Ed., Rev. 2, at 2100-128) ("The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure."). For this reason alone the rejection should be withdrawn.

We also note that the Examiner apparently interprets claim 8 to cover "phytosterols composition in combination with omega-3-fatty acids...." (Paper No. 17 at 5.) That, however, is not what is claimed. Pending claim 8 is reproduced below:

> 8. A composition comprising an admixture of the compounds (a) and (b) wherein ***(a) is a phytosterol ester compound*** produced from a reaction of a phytosterol with eicosapentaenoic acid or docosahexaenoic acid; and ***(b) is a second ester*** which is the product of an esterification reaction between a phytosterol and/or a phytostanol and (i) a fatty acid having less than 18 or more than 22 carbon atoms and at least three carbon-carbon double bonds and/or; (ii) a fatty acid having from 18 to 22 carbon atoms and less than three carbon-carbon double bonds.

In short, claim 8 rectes a composition containing an admixture of a phytosterol ester and a second, specifically-defined ester. The rejection, however, has apparently transformed the claim to cover a composition containing "sterols [and] unsaturated fatty acids" or to "phytosterols composition in combination with omega-3-fatty acids." (Paper No. 17 at 5-6.) That is not what is claimed.

Accordingly, the rejection is not directed to the subject matter recited in claim 8. For this reason also the rejection is moot and must be withdrawn.

Because the rejection misinterprets claim 8, it is silent as to the "second ester" recited in clause (b). The rejection fails to identify where in any of the cited documents these specific esters are disclosed. Nor does the rejection identify any suggestion or motivation that would lead one to the second ester recited by claim 8. For this reason as well, the rejection should be withdrawn.

Furthermore, the Examiner carried out her analysis from the vantage point of one skilled in the art *circa* April 2003 – the time the rejection was made – not just prior to the date the invention was made, as required by the statute, binding Federal Circuit precedent, and PTO rules. *See* 35 USC §103(a); *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) *quoting Panduit Corp. v. Dennison Mfg. Co.*, 1 USPQ2d 1593, 1595-96 (Fed. Cir. 1987) ("To reach a proper conclusion under §103, the decision maker ***must*** step backward in time and into the shoes worn by (a person having ordinary skill in the art) when the invention was unknown and just before it was made.") (Emphasis added.); and MPEP §2142 at 2100-128 ("To reach a proper determination under 35 USC §103, the examiner ***must*** step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made.") (Emphasis added.)

The analysis carried out by the Examiner was conducted based on knowledge at the time the ***rejection*** was made. The Examiner stated that the "[i]nstant claim ***is*** a selection of prior art teachings...." (Paper No. 17 at 5.) The Examiner also stated that "it would ***be*** obvious ... to employ phytosterols composition [sic] in

combination with omega-3-fatty acids ... because these agents ***are*** known individually for the treatment of the same disorders." (*Id.*) The Examiner also stated that "[t]he combination of agents, each of which ***is*** known for the same purpose, ***is*** considered *prima facie* obvious." (*Id.* at 6.) And, the Examiner asserted that "[m]otivation ***is*** to prepare additional beneficial composition of sterols with unsaturated fatty acids ...." (*Id.*)

The Examiner's analysis unmistakably uses verb forms of the present and present perfect tenses – "is," "would be" and "are known." The Examiner clearly analyzed the claims from the vantage point of when she wrote the rejection. *See Fine*, 5 USPQ2d at 1598. Whether claim 8 "***is*** a selection of prior art teachings," whether claim 8 "would ***be*** obvious" because phytosterols and fatty acids "***are*** known individually for the treatment of the same disorders," whether a combination of agents "***is*** considered *prima facie* obvious" and whether the "[m]otivation ***is*** to prepare [a] beneficial composition" ***are all*** irrelevant questions to a determination under §103. What the Examiner was required to do, but did not do, was to go back in time to just before the invention was made, and consider what one skilled in the art "would have known" based on Mitchell, Kamarei and Miettinen.

That the Examiner used a stock concluding paragraph correctly characterizing when the analysis should have taken place in the second rejection of the Office Action serves only to highlight that the analysis in the first rejection was impermissibly carried out at the wrong time. *See* Paper No. 17 at 8:

> It ***would have been*** obvious to one skilled in the art to prepare additional beneficial composition [sic] by selecting any fatty acids for example, docosahexaenoic acid and eicosahexaenoic acid from fatty acid 2-22 carbon atoms

> taught by the prior art. There has been ample motivation provided by the prior art to prepare the instant invention. Instant compositions ***would have been obvious at the time of invention***. The subject instantly claimed ***would have been*** obvious to one at the time of invention. (Emphasis added.)[2/]

Thus, the Examiner clearly understood when a §103 analysis should have been conducted. Just as clearly, the Examiner did ***not*** go back in time in the first rejection to carry out the analysis. Because the Examiner failed to conduct the obviousness analysis from the vantage point of one skilled in the art just prior to the time the invention was made, the rejection of claim 8 is both legally and factually deficient and should be withdrawn for this reason as well.

The Examiner also failed to identify where in the cited documents the motivation to combine them in the manner suggested is found. The Examiner's apparent basis for the required motivation rests solely on two sentences containing an unsupported allegation that one would be motivated to prepare "additional beneficial composition[s] of sterols."

> Motivation is to prepare additional beneficial composition [sic] of sterols with unsaturated fatty acids such as omega-3-fatty acids, EPA, DHA, useful for lowering the cholesterol and triglyceride levels, because this use has been taught by the prior art for the said compositions. Preparation of supplemental vitamins, margarine and mayonnaise is taught by the prior art cited above. (Paper No. 17 at 6.)

The Examiner failed to cite with specificity to any of the three documents asserted in the rejection, relying instead on generalized statements attributed to "the prior art." Thus, one is left to guess at the source, if any, of the motivation. As is well

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2/ We note that the rejection refers to "eicosahexaenoic acid," we assume, however, that the Examiner intended "eicosapentaenoic acid." If this assumption is incorrect, we request that the Examiner

settled, however, the Examiner was required to conduct a thorough and searching factual inquiry into whether to combine the cited references. *See McGinley v. Franklin Sports, Inc.*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). The Examiner was also required to specifically identify the basis for her assertion of motivation. *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) ("The need for specificity pervades this authority."); *see also In re Rouffet*, 47 USPQ2d at 1459 ("The Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."). The Examiner's burden in this regard is met only by showing evidence from the prior art or generally available knowledge that would lead one to make the proposed combinations. *In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

The Examiner failed to identify where in Mitchell, Kamarei, and Miettinen there is a disclosure or suggestion that a phytosterol ester made from EPA or DHA would be useful for any purpose. Indeed, the Examiner completely ignored the disclosure in Kamarei that administration of EPA - not even an ester of EPA - caused undesirable side effects, such as, increased bleeding time and decreased platelet aggregation. (Col. 2, lines 56-59.)

Moreover, the Examiner failed to explain why Kamarei is even combinable with Mitchell and Miettinen. In this regard, we note that Kamarei, as a whole, is directed to promoting/enhancing angiogenesis - not treating high cholesterol levels using various phytosterol esters as described in Miettinen or administering steroid and hormone precursors using various phytosterol esters as set forth in Mitchell. Thus, it was the

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confirm on the record that "eicosahexaenoic acid" was intended. This error occurs repeatedly in the rejections and will not be addressed again in this Response.

Examiner's burden to explain why one skilled in the art would look to an angiogenesis document when deciding which fatty acid to react with a phytosterol to produce a phytosterol ester compound. This the Examiner did not do.

In addition, the Examiner is simply mistaken that "the prior art" provides any motivation is "to prepare additional beneficial composition of sterols with unsaturated fatty acids such as omega-3-fatty acids, EPA, DHA, useful for lowering the cholesterol." (Paper No. 17 at 6.) About eleven months after the filing of the above-captioned application, the FDA published a thorough review of the scientific literature regarding health claims for omega-3 fatty acids and coronary heart disease that concluded that omega-3 fatty acids (*i.e.*, DHA and EPA) were not known to lower cholesterol levels. *Letter Regarding Dietary Supplement Health Claim or Omega-3 Fatty Acids and Coronary Heart Disease* (October 31, 2000) ("FDA Letter") (Exhibit A).[3/] In the letter, the FDA concluded that there was no support for a claim that omega-3 fatty acids lower cholesterol levels.

> The agency also considered the scientific evidence from a number of intervention studies relating intake of omega-3 fatty acids to levels of LDL cholesterol, a validated surrogate marker for CHD risk (Table 2). ***Most of the intervention studies that measured blood lipids, both in general and diseased populations, reported no significant differences in LDL cholesterol.*** Several of these intervention studies reported increased levels of LDL cholesterol. [One] reported decreased levels of LDL cholesterol in response to intake of omega-3 fatty acids in dietary supplements. Thus, ***most of the intervention studies that measured LDL cholesterol did not support a relationship between omega-3 fatty acids and reduced risk of CHD either in diseased or general populations.***
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> In particular, the GISSI trial (GISSI Prevensione Investigators, 1999), the clinical trial with the longest

3/ Available on the FDA website at: http://www.cfsan.fda.gov/~dms/ds-ltr11.html.

> duration (3.5 years), the largest sample size (n = 11,324), and that measured both LDL cholesterol and CHD in a diseased population, ***reported that there were no statistically significant changes in LDL cholesterol, while also reporting a 15-percent-decrease in relative risk of CHD in the diseased population intervention group that consumed omega-3 fatty acids*** (Tables 1 and 2). Thus, in most of the intervention studies, including the GISSI trial with the largest sample size and the longest duration, omega-3 fatty acids ***showed a reduction of risk for CHD in a diseased population, but the effect is apparently not working through a mechanism of LDL cholesterol reduction***. (Page 9.)

Accordingly, one of ordinary skill in the art at the time of filing of the present application would not have concluded, based on the prior art, that omega-3 fatty acids lower cholesterol levels.

The Examiner also relies on *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), to explain the basis of the motivation to combine the cited documents. However, the Examiner's reliance on *Kerkhoven* is also misplaced. In *Kerkhoven*, the CCPA held that the mere mixing together of two known detergent components in a process for preparing a detergent composition, without more, was obvious. 205 USPQ at 1072. Those are not the facts here. The present claims are directed to compounds, not processes as recited in *Kerkhoven*. The claimed phytosterols and phytostanols are chemically reacted with EPA and DHA – they are not simply mixed together as in *Kerkhoven*. Moreover, one of the cited documents – Kamarei – specifically discloses that EPA has negative side effects (*i.e.*, increased bleeding time and decreased platelet aggregation). And, contrary to the Examiner's assertion, EPA and DHA were not known in the prior art to lower cholesterol.

Indeed, the present case is much like the facts in *Ex parte Bokisa*, wherein the Board distinguished *Kerkhoven* and reversed a §103 rejection, in part, because the claimed invention was not merely a mixing together of known compositions and, in part, because the cited art taught away from the claimed invention. See 1997 WL 1897871, *2-*3 (BPAI 1997) (unpublished); *See also Ex parte Garfield*, 2004 WL 77127, *3 (BPAI 2004) (unpublished) (distinguishing *Kerkhoven* and reversing a § 103 rejection because the cited art failed to disclose all of the elements recited in the rejected claims).

In short, the Examiner's two sentence basis for motivation and her reliance on *Kerkhoven* are simply insufficient to meet her burden. Accordingly, for this reason as well, the rejection is legally and factually deficient and should be withdrawn.

For the reasons set forth above, the rejection of claim 8 should be withdrawn.

Claims 1-4, 24, and 25 were rejected under 35 USC §103 as unpatentable over Miettinen and Mitchell. (Paper No. 17 at 6.)

For the reasons set forth below the rejection, respectfully is traversed.

Miettinen and Mitchell are summarized above.

In making the rejection, the Examiner relied on virtually the same characterizations of Miettinen and Mitchell. (*Id.* at 6-7.) The Examiner acknowledged, however, that the rejected claims differed from Miettinen and Mitchell in the recitation of "specific fatty acids" – EPA and DHA. (*Id.* at 7.) Again, the Examiner characterized the rejected claims as nothing more than a "selection of prior art teachings."

> Instant claims are a selection of prior art teachings. (*Id.* at 8).

The Examiner then concluded that it would have been obvious to make the claimed compounds/compositions by making the appropriate selection of fatty acids based on the "ample motivation" provided by the "prior art."

> It would have been obvious to one skilled in the art to prepare additional beneficial composition by selecting any fatty acids for example, docosahexaenoic acid and eicosahexaenoic acid from fatty acid 2-22 carbon atoms taught by the prior art. There has been ample motivation provided by the prior art to prepare the instant invention. Instant compositions would have been obvious at the time of invention. The subject as instantly claimed would have been obvious to one at the time of invention. (Id.)

As is fundamental, "[t]o establish a *prima facie* case of obviousness ... the prior art reference must teach or suggest all the claimed limitations." *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974) and MPEP 706.02(j), 2143, and 2143.03 (8th Ed., Rev. 2, pp. 700-46, 2100-129, and 2100-133-134). Additionally, a *prima facie* case of obviousness must be based on facts. *In re Freed*, 165 USPQ 570, 571-72 (C.C.P.A. 1970). When the rejection is not supported by facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d at 1474. A *prima facie* case of obviousness also requires that the rejection describe with specificity why one skilled in the art would have combined the references to arrive at the claimed invention. *In re Dembiczak*, 50 USPQ2d at 1617.

Similar to the rejection of claim 8, the Examiner was dismissive of the rejected claims:

> Instant ***claims are a selection of prior art teachings***. (Emphasis added.) (*Id.* at 8.)

As noted above, whether or not the elements of a claimed invention can be selected from among various pieces of prior art, is however, irrelevant to an obviousness

analysis.

The Examiner asserted that Mitchell and Miettinen disclose or suggest incorporating EPA or DHA into a phytosterol ester. The Examiner observed generically that the "prior art teaches the reaction product of phytosterol with fatty acids especially containing approximately 2-22 carbon atoms." (*Id.*)

The Examiner's citation to Miettinen actually discloses methyl esters or mixtures thereof from "***any*** vegetable oil, especially of fatty acids which contain approximately 2-22 carbon atoms." (Emphasis added.) (Page 10, lines 20-25 and page 9, lines 22-30.) And, the Examiner failed to identify where in Miettinen EPA or DHA, as claimed, is specifically identified or even suggested as being a good choice for esterification with sterol/stanols.

Moreover, Mitchell simply does not disclose or suggest what the Examiner says it does – EPA and DHA. Rather, Mitchell discloses reacting a phytosterol with essentially ***any*** fatty acid. Mitchell does specifically identify fatty acids having from "about 18 to about 20 carbon atoms," such as for example, "linoleic acid," "linolenic acid," and "arachidonic acid." (*See e.g.*, col. 5, lines 55-66). Mitchell also discloses that fatty acids "having less than 18 carbon atoms" or "more than 20 carbon atoms ... may be used," but that such fatty acids "tend to have less utility." (Col. 6, lines 9-15). Here too, the Examiner failed to identify where in Mitchell EPA or DHA are specifically identified or suggested.

In sum, it is the rejection – ***not*** the claims – which is based on a "selection of prior art." (Paper No. 17 at 8.) As noted above, it was the Examiner's burden to provide evidence showing why one would have been motivated to choose DHA or EPA

based on the generic disclosure of "any fatty acid," C_{2-22} fatty acids, and C_{18-20} fatty acids cited in the documents applied by the Examiner. Without such evidence, the only conclusion is that the Examiner used Appellants' specification as a blueprint to navigate from the disclosures to EPA and DHA as claimed. But, such hindsight reconstruction is not permitted. For this reason alone, the rejection should be withdrawn.

The Examiner also failed to show where in the cited documents the motivation to combine them in the manner suggested is found. Because the Examiner failed to identify such evidence, she has not met her burden and the rejections should be withdrawn.

The Examiner's sole basis for the required motivation rests on a nebulous assertion of "ample motivation provided by the prior art."

> There has been ample motivation provided by the prior art to prepare the instant invention. (*Id.* at 8.)

However, the Examiner cites only to the "prior art" generally for the motivation to combine the disclosures of Miettinen and Mitchell. Attributing the alleged "ample motivation" to the "prior art," without more, is not the kind of thorough and searching analysis required by *McGinley*. An allegation that the prior art provides "ample motivation," without more, is not the kind of specificity demanded by *Lee*. And, reliance on an allegation of "ample motivation" avoids the requirement for evidence commanded by *Fritch*. At bottom, the Examiner's single sentence basis for motivation is insufficient to meet her burden. Accordingly, the rejection should be withdrawn for this reason as well.

Further, the Examiner misconstrued the scope of Mitchell and Miettinen. The Examiner acknowledged that Mitchell and Miettinen did not specifically disclose EPA and DHA as recited in claims 1-4, 24, and 25. (Paper No. 17 at 7-8.) The Examiner asserted, however, that Mitchell and Miettinen disclosed a reaction product of a phytosterol with fatty acids containing 2-22 carbon atoms. (*Id.* at 8.) The Examiner then concluded that the "[i]nstant claims are a selection of prior art teachings." (*Id.*)

Thus, the rejection is predicated on the Examiner's conclusion that the disclosure of fatty acids containing C_{2-22} carbon atoms somehow identifies or suggests EPA and DHA. It appears that the sole basis for the Examiner's conclusion that the disclosure of C_{2-22} fatty acids suggests EPA and DHA is that these specific compounds "would have been obvious."

> ***It would have been obvious*** to one skilled in the art to prepare additional beneficial composition by selecting any fatty acids for example, docosahexaenoic acid and eicosahexaenoic acid from fatty acid 2-22 carbon atoms taught by the prior art. There has been ***ample motivation*** provided by the prior art to prepare the instant invention. Instant compositions would have been obvious at the time of the invention. The subject as instantly claimed would have been obvious to one at the time of the invention. (Emphasis added.) (*Id.*)

As the Examiner acknowledged, neither Mitchell nor Miettinen specifically disclose EPA or DHA. Even though Mitchell expresses a preference for C_{18-20} fatty acids, the Examiner ignored clear disclosure in Mitchell suggesting that ***any*** fatty acid could be used to make the steroid vitamin supplements:

> Although **fatty acids having less than 18 carbon atoms ... or more than 20 carbon atoms ... may be used,** it has been found that phytosterol esters made from such fatty acids tend to have less utility in achieving the purposes of

the present invention. (Emphasis added.) (Col. 6, lines 9-15.)

And, even within the preferred C_{18-20} family of fatty acids, Mitchell identifies and exemplifies only linoleic acid, linolenic acid, and arachidonic acid. (*See* Col. 5, lines 64-66 and Examples 1-75.)

The Examiner also misinterpreted Miettinen. Miettinen broadly discloses that ***any*** vegetable oil or ***any*** C_{2-22} fatty acid may be used to obtain the phytosterol ester.

> A methyl ester mixture of the fatty acids of ***any*** vegetable oil can be used in the reaction .... ***any*** fatty acids which contain approx. 2-22 carbon atoms are usable. (Emphasis added.) (Page 6, lines 30-34.)
>
> * * * *
>
> Instead of a mixture of rapeseed oil fatty acid esters it is possible to use ... fatty acids which contain approximately 2-22 carbon atoms. (Page 10, lines 20-24.)

In short, Miettinen does not disclose any particular fatty acid. Rather, Miettinen identifies "any" oil and "any" C_{2-22} fatty acid in general and rapeseed oil in particular as a source of the fatty acids.

The Examiner did not identify any disclosure from Mitchell or Miettinen that would suggest using EPA or DHA as the source of the fatty acid component of a phytosterol ester as claimed. Nor did the Examiner even attempt to reconcile the apparent conflict between the narrow preferred range of fatty acids disclosed in Mitchell (C_{18-20}) and its disclosure that fatty acids with less than 18 or more than 20 carbon atoms have less utility and the broad teachings of Miettinen that any C_{2-22} fatty acid may be used. Nor did the Examiner attempt to reconcile the fact that DHA, a 22 carbon atom fatty acid falls outside the preferred Mitchell range.

The rejection relies on two disclosures that recite conflicting ranges of preferred fatty acids, that do not recite either of the two claimed fatty acids, and that provide no suggestion or motivation to select the two claimed fatty acids. Recognizing the insufficiency of this evidence, the Examiner is reduced to relying on the bald assertions that EPA and DHA "would have been obvious" and that "ample motivation" has been provided by the prior art. (Paper No. 17 at 8.)

In sum, the Examiner failed to identify where in Mitchell and Miettinen there is a disclosure that would have suggested or motivated one to use EPA or DHA. Indeed, the Examiner failed to explain why one would even consider DHA in view of Mitchell's disclosure that fatty acids having more than 20 carbon atoms have less utility. Thus, the rejection is factually deficient and cannot stand for this reason as well.

Moreover, it was the Examiner's burden to identify disclosures from Mitchell or Miettinen or technical reasoning that would have filled the acknowledged gap in these documents. This the Examiner did not do. The use of "would have been obvious" or "ample motivation" is no substitute for the required factual showing of a disclosure that is sufficient to have suggested or motivated one skilled in the art to have selected EPA or DHA as claimed. Here, the Examiner failed to identify on what basis one would have concluded that EPA and DHA would have been obvious choices based on Mitchell or Miettinen or from where the alleged "ample motivation" arises. In the absence of such evidence, the rejection is deficient and must be withdrawn for this reason too.

Further, as is well settled, the disclosure of a genus does not render a species or a subgenus obvious. *In re Jones*, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992)

("Conspicuously missing from this record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have been motivated to make the modifications of the prior art salts necessary to arrive at the claimed 2-(2'-aminoethoxy) ethanol salt.... We conclude that the PTO did not establish a *prima facie* case of obviousness."); *In re Baird*, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.).

The Examiner's sole basis for rejecting the claims is that "it would have been obvious" to use EPA and DHA based on fatty acids containing 2-22 carbon atoms "taught by the prior art." (*See* Paper No. 17 at 6.) The Examiner's unstated rationale for this conclusion appears to be that the genus of C_{2-22} fatty acids renders obvious two species – EPA and DHA.

The rejection completely ignores clear precedent that something more than a broad recitation of a generic formula is required to render obvious a species or a subgenus encompassed by a generic formula. At best, the rejection points to the disclosure of C_{2-22} fatty acids. However, the rejection is simply devoid of any evidence that supports the conclusion that there is "ample motivation" in the art to go from the genus of C_{2-22} fatty acids to EPA and DHA. And, although it is not our burden, we note that there is no disclosure in either Miettinen or Mitchell that would lead one from this broadly disclosed genus of fatty acids to EPA and DHA specifically. For this additional reason, the rejection should be withdrawn.

We also note that the rejection completely ignores an element of claims 1 and 24. Specifically, the rejection identifies nothing in Miettinen or Mitchell, alone or in

combination, that discloses or suggests that the compound is a liquid between about -20°C and 20°C. Thus, the rejection contains an additional (unacknowledged) factual gap. For this additional reason, the rejection should be withdrawn as to claims 1-4 and 24.

Furthermore, the Examiner completely ignored claims 24 and 25, and thus, failed to engage in the analysis required to support a *prima facie* rejection for obviousness. For example, the rejection failed to consider claims 24 and 25 as a whole. The rejection failed to identify the differences between claims 24 and 25 and the cited documents. And, the rejection failed to engage in any analysis relating to whether the inventions recited in claims 24 and 25, as a whole, would have been obvious. That, however, was the Examiner's burden. *See Graham v. John Deere Co.*, 383 US 1, 17-18, 148 USPQ 459, 467 (1966); and MPEP §2141 (8th Ed, Rev. 2, pp. 2100-120) ("Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 USC §103.")

Because claims 24 and 25 were ignored, the Examiner did not acknowledge the specific physical properties of the phytostanol ester (*i.e.*, that it is liquid at temperatures from -20° to 20°C) recited in claim 24. Nor did the Examiner acknowledge that the compound of claim 25 was produced from a reaction of EPA or DHA with a mixture of phytosterol and phytostanol.

The Examiner made no findings with respect to the phase (*i.e.*, solid, liquid, or gas) of the ester between -20°C to 20°C disclosed in Mitchell and Miettinen. Nor did the Examiner make any findings with respect to the nature of the esters formed from the reactions described in Mitchell and Miettinen and the nature of the claimed

compound recited in claim 25. And, the Examiner made no finding with respect to why one skilled in the art would have believed that the compounds recited in claims 24 and 25, as a whole, would have been obvious in view of the disclosures of Miettinen alone, or in combination with, Mitchell. For this reason too, the rejection of claims 24 and 25 should be withdrawn.

For the reasons set forth above, the rejection of claims 1-4, 24, and 25 should be withdrawn.

Claims 1-4, 8, 24, and 25 were newly rejected under 35 USC §103(a) as being unpatentable over Higgins, III, U.S. Patent No. 6,147,236 ("Higgins '236") and Higashidate *et al.*, J. of Chromatography, 515: 295-303 (1990) ("Higashidate"). (Paper No. 06272004 at 5.)

For the reasons set forth below the rejection, respectfully is traversed.

Higgins '236 discloses a "method for the direct esterification of stanols and sterols with fatty acids to form stanol/sterol-esters." (Abstract.)

Higashidate discloses that "[m]ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in esterified fish oils were extracted by supercritical fluid extraction with carbon dioxide and directly introduced into a silica gel column coated with silver nitrate." (Abstract.)

In making the rejection, the Examiner asserted that the cited documents disclose "sterol esters and methyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which embrace instantly, claimed invention." (Paper No. 06272004 at 5.) The Examiner acknowledged, however, that the "[i]nstant claims differ from the [cited document] in claiming a nutritional supplement of specific sterol esters

prepared by unsaturated fatty acid esters selected from EPA, DHA, and Stearidonic acid (SA) whereas prior art [Higgins '236 discloses] sterol esters with unsaturated fatty acids, examples given is same as one of the instantly claimed sterol ester, *i.e.* sterol with DHA, sitosterol docosahexaenoate, and sitostanol docosahexaenoate...." (*Id.* at 5-6.)

To fill the acknowledged gap, the Examiner relied upon Higashidate as disclosing "DHA and EPA from fish oils and prevent diseases such as arteriosclerosis and myocardial infarction by lowering the concentration of lipids and cholesterol in blood." (*Id.* at 6.) The Examiner also asserted that Higashidate "discloses that fish oil is a rich source of such fatty acids." (*Id.*)

The Examiner then concluded that "it would have [been] obvious ... to prepare additional beneficial nutritional supplement using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent." (*Id.*) The Examiner also asserted that because Higgins '236 discloses "such sterol esters" and Higashidate discloses "that fish oil contains omega-3 fatty acids (a class of PUFA) which includes docosahexaenoic acid (DHA) and eicosahexaenoic acid (EPA), one would find ample motivation to prepare sterol esters with unsaturated fatty acids from active compounds present in fish oil (known to be used as nutritional supplement to lower the cholesterol and triglyceride levels) or using unsaturated fatty acids from any other source lowering the cholesterol and triglyceride levels." (*Id.*)

Initially, we note that when a rejection relies on an issued U.S. patent claiming benefit to an earlier filed application as a ***continuation-in-part***, it is incumbent upon the Examiner to make the necessary factual determinations as to whether the

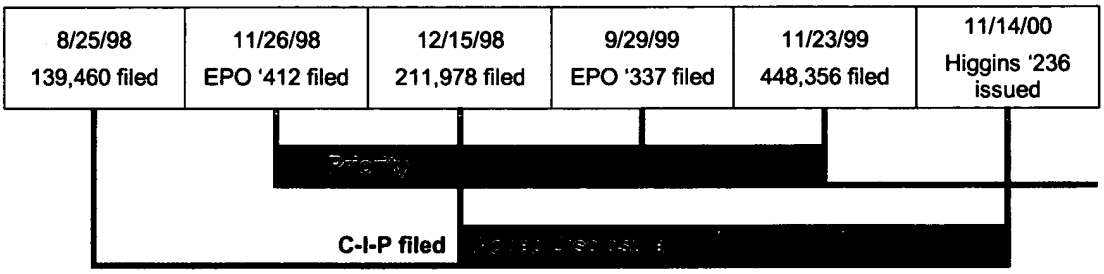
subject matter in the patent asserted is supported by the earlier filed application, *i.e.*, complies with the requirements of § 112, first paragraph. 35 USC § 120. Where, as here, the rejection fails to make these factual determinations, the rejection is insufficient as a matter of law and must be withdrawn. *Ex parte Saceman*, 27 USPQ2d at 1474 (When a conclusion of obviousness is not based upon facts, it cannot stand.); *In re Freed*, 165 USPQ at 571-72. (Obviousness ***must*** be based upon facts, "cold hard facts.").

Notwithstanding the infirmities noted above, and although it is not our burden, we demonstrate below that the Examiner is ***not*** entitled to rely on the August 25, 1998 filing date of Higgins, III, U.S. Patent No. 5,892,068 ("Higgins '068") in the present rejection because the subject matter relied upon in the rejection was not described or enabled in 09/139,460 ("'460 application).

The present application claims priority under 35 USC § 119 to EPO 98122412.4 ("EPO '412"), filed November 26, 1998, and to EPO 99119337.6, filed September 29, 1999. The subject matter of claims 1-4, 8, 24, and 25 is fully supported and enabled by the disclosure of EPO '412 and is therefore entitled to benefit of its November 26, 1998 filing date. *Transco Products, Inc. v. Performance Contracting Inc.*, 32 USPQ2d 1077 (Fed. Cir. 1994). And, the Examiner has not – indeed, cannot – make a finding of fact that claims 1-4, 8, 24, and 25 are not entitled to benefit of EPO '412.

Higgins '236 has a filing date of December 15, 1998. Higgins '236 is a ***continuation-in-part*** of the '460 application, filed August 25, 1998, which matured into Higgins '068, which issued April 6, 1999. As is well settled, an application which is a

continuation-in-part of an earlier application may claim priority to the earlier application only for the subject matter fully disclosed and enabled in the earlier application. *Transco Products* at 1082 n. 6; *see also*, MPEP § 2133.01 (8th Ed., Rev. 2, p. 2100-80). Any newly added subject matter can only claim priority back to the filing date of the later application. For the Examiner's convenience, a timeline for the respective priority dates is set forth below.



The subject matter relied on by the Examiner to make the rejection is not disclosed in Higgins '068. A comparison of the two patents demonstrates that the disclosure relied upon by the Examiner to make the rejection, was not present in the earlier application and was, therefore, new to Higgins '236. Attached is a computer comparison of the text of the two patents.[4/] (Exhibit B.) In this comparison, the Higgins '068 patent is used as the base and the notations indicate the differences found in Higgins '236. Blue double underline indicates additions to, and ~~red strike-through~~ indicates deletions from Higgins '068. Also attached is a copy of the issued version of Higgins '236 in which the added material is highlighted.[5/] (Exhibit C.) A review of the

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[4/] The text of the two patents was taken from the USPTO website. (*See*, **http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=5,892,068.WKU.&OS=PN/5,892,068&RS=PN/5,892,068**, and **http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=/netahtml/srchnum.htm&r=1&f=G&l=50&s1=6,147,236.WKU.&OS=PN/6,147,236&RS=PN/6,147,236**.)

[5/] Apparent corrections of typographical errors, other minor changes, and differences in the claims, which are immaterial to this discussion, have not been highlighted.

added material conclusively demonstrates that the very subject matter relied upon by the Examiner to make the present rejection, was new to Higgins '236.

The Examiner's apparent reliance upon the August 25, 1998, filing date of Higgins '068 is misplaced. The subject matter the Examiner relied upon to make the rejection has a filing date of ***December 15, 1998***. Accordingly, the subject matter relied upon by the Examiner is not prior art to claims 1-4, 8, 24, and 25 and cannot be relied upon by the Examiner in making a § 103 rejection. Hence, the primary document relied upon by the Examiner has been removed creating a fatal factual gap in the rejection.

The Examiner has not demonstrated that this gap can be filled by Higashidate. Higashidate discloses the separation of DHA and EPA methyl esters from esterified fish oil. Nowhere in Higashidate is there any disclosure of the esterification of any compound. The only esters even disclosed in Higashidate are methyl esters of DHA and EPA, which are separated.

The methyl ester compounds of Higashidate do not have a sterol functionality and have molecular weights more than 200 less than the corresponding sterol/stanol ester. (*See* Table 1, below.)

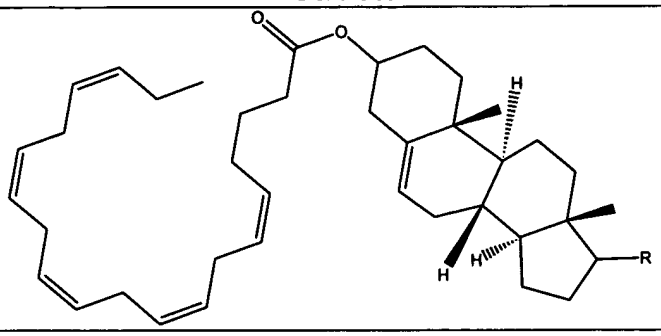
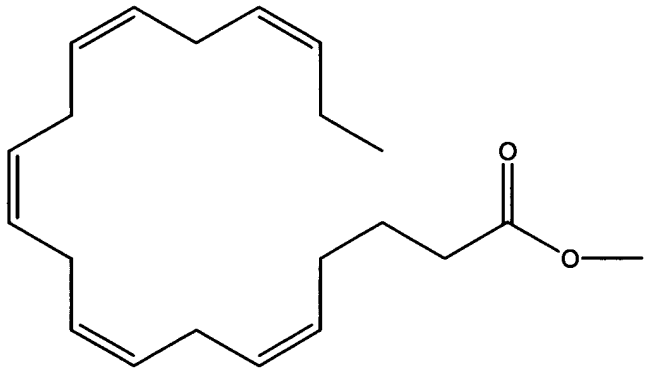
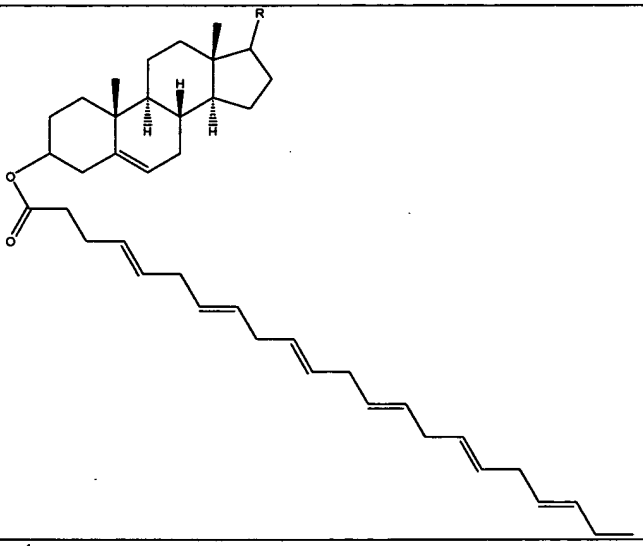
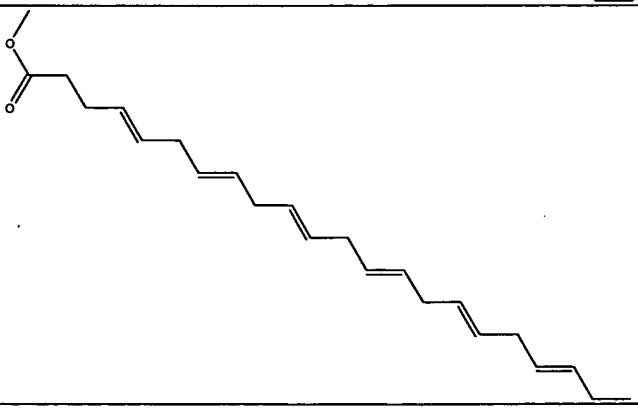
Compound	Structure	M.W.
EPA-sterol/stanol ester		> 558
EPA-methyl ester		316.48
DHA-sterol/stanol ester		> 584
DHA-methyl ester		342.51

Table 1. Comparison of EPA/DHA-sterol/stanol esters to EPA/DHA-methyl esters

Moreover, there is no disclosure or suggestion of any use for the isolated methyl esters of DHA and EPA. Higashidate merely discloses the separation of the compounds. And, given the structural differences between the molecules there is no reason for one of skill in the art to conclude that they would share the same properties as the sterol/stanol esters.

For the reasons set forth above, the rejection of claims 1-4, 8, 24, and 25 should be withdrawn.

Claims 1-4, 8, 24, and 25 were also newly rejected under 35 USC § 103 as unpatentable over Mitchell, Mishkel *et al.*, Baillière's Clinical Haematology, Vol. 3, No. 3, pp. 625-649 (1990) ("Mishkel"), and Kamarei. (Paper No. 06272004 at 6.)

For the reasons set forth below the rejection, respectfully is traversed.

Mitchell and Kamarei are summarized above.

Mishkel is a chapter from a clinical hematology textbook. The "purpose of [the] chapter is to review the salient studies of fish oils and their application to human cardiovascular disease." (Abstract.) Mishkel also discloses that fish oil and omega-3 fatty acids appear to have beneficial effects on cardiovascular health. *See e.g.*, pp. 626, 1st ¶ and 628, 2nd ¶.

In making the rejection, the Examiner characterized Mitchell and Kamarei as she had in the rejections found in Paper No. 17 discussed above.

The Examiner asserted that Mishkel discloses that "fish oil containing omega-3 fatty acids lower the serum and cholesterol levels, and their beneficial effect on preventing and treating cardiovascular disease. See 1st Para on page 626, third paragraph on page 629, second Para on page 628." (Paper No. 06272004 at 7.) The

Examiner also asserted that Mishkel discloses "[s]pecific use of DHA and EPA as dietary supplement ... on section 'Angina' on page 634." (*Id.*)

The Examiner acknowledged, however, that "the instant claims differ from the [cited documents] in claiming a nutritional supplement of phytosterol ester with specific fatty acids i.e. docosahexaenoic acid, stearidonic acid and eicosahexaenoic acid, where [Mitchell discloses] phytosterol ester with fatty acids especially containing poly unsaturated fatty acid approximately 2-22 carbon atoms." (*Id.* at 8.)

To fill the acknowledged gap, the Examiner relied on Mishkel as disclosing "that polyunsaturated fatty acids from fish oil is used to [sic] preventing and treating cardiovascular disease" and "two major biologically active fish oil compounds, EPA and DHA." (*Id.*) In addition, the Examiner relied on Kamarei as disclosing that "n-3 PUFA *i.e.* eicosapentaenoic acid (EPA) and DHA reduces triglyceride and very low-density lipoprotein (VLDL) serum levels and reduces whole blood viscosity." (*Id.*)

The Examiner concluded that "it would have been obvious ... to prepare additional beneficial nutritional supplement using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent." (*Id.*)

As previously noted, the Examiner bears the burden to set forth a *prima facie* case of unpatentability, and if the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

The rejection concludes that "it would have been obvious ... to prepare additional beneficial nutritional supplement using sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent." (Paper No. 9 at 8.) However, an "additional beneficial nutritional supplement using

sterols with a pendent ester functionality which when hydrolyzed provides another cholesterol-lowering agent" is not what is claimed. Claim 1 recites a "phytosterol ester compound produced from a reaction of a phytosterol with eicosapentaenoic acid or docosahexaenoic acid...." Claim 8 recites a "composition comprising an admixture of the compounds (a) and (b) wherein (a) is a phytosterol ester ... and (b) is a second ester which is the product of an esterification reaction between a phytosterol and/or a phytostanol and" a fatty acid. Claim 24 recites a "phytostanol ester compound produced from a reaction of a phytostanol with eicosapentaenoic acid or docosahexaenoic acid...." Claim 25 recites a "compound produced from a reaction of eicosapentaenoic acid or docosahexaenoic acid with a mixture of phytosterol and phytostanol...." Because the rejection does not reject that which is claimed, it is both legally and factually deficient and must be withdrawn.

The rejection also fails to identify why one skilled in this art would have combined the disclosures of Mitchell, Mishkel, and Kamarei in the manner suggested to arrive at the claimed invention. Mitchell discloses phytosterol ester compounds and their use in vitamin supplements. Mishkel discloses that fish oil and omega-3 fatty acids are beneficial to cardiovascular health. And, Kamarei discloses a method of causing or increasing angiogenesis by administering effective amounts of omega-3 fatty acids.

Nothing in Mishkel or Kamarei discloses or suggests the esterification of any compound, much less a phytosterol. Mishkel and Kamarei merely disclose that omega-3 fatty acids are useful in treating and preventing cardiovascular disease. That omega-3 fatty acids are beneficial to cardiovascular health would not lead one to

conclude that these compounds should be esterified or in any other way modified. Mishkel and Kamarei disclose that these compounds are effective in their natural, unaltered state.

In addition, the Examiner is mistaken in asserting that Mishkel discloses that "fish oil containing omega-3 fatty acids lower the serum and cholesterol levels." (Paper No. 06272004 at 7.) The Examiner points to page 626, paragraph 1. However, the paragraph discusses the prevalence of cardiovascular disease among an Eskimo population. The paragraph says absolutely nothing about serum cholesterol levels. The Examiner also points to the second paragraph on page 628. This paragraph discusses a study of the effect of dietary ω-3 fatty acid supplements in swine. Contrary to the Examiner's assertion, the cholesterol levels in both the treated and placebo groups ***rose***.

> For the next 8 months [the swine] were maintained on the high cholesterol diet and were randomized to receive 30 ml of cod liver oil (3.6 g EPA) daily or placebo. In both groups total plasma cholesterol, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and high-density lipoproteins (HDL) rose significantly ... The beneficial changes seen with the fish oil were independent of any specific positive effect on lipids.

Moreover, as discussed above, an FDA review of the scientific evidence available at the time of invention concluded that there was no support for a claim that omega-3 fatty acids lower cholesterol levels:

> Thus, ***most of the intervention studies that measured LDL cholesterol did not support a relationship between omega-3 fatty acids and reduced risk of CHD either in diseased or general populations***.
>
> * * *

> Thus, in most of the intervention studies, including the GISSI trial with the largest sample size and the longest duration, omega-3 fatty acids ***showed a reduction of risk for CHD in a diseased population, but the effect is apparently not working through a mechanism of LDL cholesterol reduction***. (FDA Letter, page 9.)

Accordingly, there is nothing in the cited documents, and the Examiner has offered no evidence or technical reason, why one would have been led combine the cited documents as suggested. And, one of skill in the art familiar with the scientific evidence available at the time of filing of the present application would not have concluded that omega-3 fatty acids lower cholesterol levels. Thus, the Examiner has failed to meet the burden to present a *prima facie* for obviousness. For this additional reason, the rejection is deficient and must be withdrawn.

Notwithstanding the forgoing, even if the combination of the cited documents is proper, which is not conceded, Mitchell, Mishkel, and Kamarei, even in combination, do not teach the claimed invention. Mitchell discloses phytosterol esters in vitamin supplements. Mishkel and Kamarei disclose the beneficial effects of omega-3 fatty acids. In combination, the cited documents, at best, suggest the admixture of the phytosterol esters of Mitchell with omega-3 fatty acids in a vitamin supplement. That, however, is not what is claimed. Accordingly, even in combination, Mitchell, Mishkel, and Kamarei do not disclose or suggest the claimed composition. For this reason too, the rejection is deficient and must be withdrawn.

For the reasons set forth above, the rejection of claims 1-4, 8, 24, and 25 should be withdrawn.

In view of the foregoing, favorable action on the merits, withdrawal of each of the rejections, and allowance of all the claims, respectfully, are solicited. If the

Examiner has any questions regarding this paper, please contact the undersigned attorney.

Respectfully submitted,

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I hereby certify that this Information Disclosure Statement, is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 28, 2005.

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